

## Dosage of Sugammadex in morbidly obese patients

Sugammadex in morbidly obese patients

Dilsen Hatice Ornek<sup>1</sup>, Aysu Hayriye Tezcan<sup>2</sup>, Hulya Ozden Terzi<sup>1</sup>, Baris Dogu Yildiz<sup>3</sup><sup>1</sup> Department of Anesthesiology and Reanimation, Ankara Numune Education and Research Hospital, Ankara<sup>2</sup> Department of Anesthesiology, Kafkas University, School of Medicine, Kars<sup>3</sup> Department of General Surgery, Ankara Numune Education and Research Hospital, Ankara, Turkey

### Abstract

**Aim:** The aim of the present study was to compare the doses of sugammadex based on ideal body weight, corrected body weight or actual body weight in terms of reversal of neuromuscular blockade and recovery of cognitive function.

**Material and Methods:** Sixty morbidly obese patients scheduled for laparoscopic sleeve gastrectomy (LSG) were studied. Patients were randomly divided into three groups and received sugammadex according to IBW, CBW or ABW. BIS and acceleromyography were used in addition to routine monitoring. All patients received total intravenous anesthesia during the operation. Neuromuscular reversal times and cortical recovery times were recorded after administration of sugammadex for recovery from anesthesia.

**Results:** Eye opening times were not statistically different between groups. The time to TOFR to 0.9, time to extubation was shortest in Group ABW and these times were longest in Group IBW. Cognitive recovery markers differed significantly among groups. The time to reach a BIS level above 80 was 160 s in Group ABW, 231 s in Group CBW and 290 s in Group IBW ( $p=0.024$ ). Time to first verbal answer to questions and time to orientation were significantly longest in Group IBW and shortest in Group ABW. Among the three groups, none of the patients had a delayed discharge from PACU secondary to respiratory complications.

**Discussion:** The ideal dosing regimen for administration of sugammadex to obese patients is still unclear. We suggest that TBW might be more appropriate for calculating sugammadex dose for safe and effective reversal of moderate rocuronium-induced neuromuscular block in morbidly obese patients.

### Keywords

Sugammadex; Obesity; Neuromuscular Block

DOI: 10.4328/ACAM.20128 Received: 2020-02-04 Accepted: 2020-02-24 Published Online: 2020-03-07 Printed: 2020-04-01 Ann Clin Anal Med 2020;11(Suppl 1): S52-S56

Corresponding Author: Dilsen Hatice Ornek, Department of Anesthesiology and Reanimation, Ankara Numune Education and Research Hospital, Ankara, Turkey.

E-mail: dilsenbaris@gmail.com / dilsenpinar@yahoo.com GSM: +90 505 737 38 28

Corresponding Author ORCID ID: <https://orcid.org/0000-0002-3300-4839>

## Introduction

The rates of surgical operations for morbid obesity (BMI >40 mg.kg<sup>-2</sup>) are steadily increasing worldwide due to ineffective medical and nutritional therapies [1]. These patients are at increased risk for postoperative complications because of concomitant metabolic comorbidities, cardiovascular diseases, and decreased pulmonary function [2]. Moreover, unpredictable effects of drugs constitute an additional postoperative risk factor in morbidly obese patients, namely insufficient recovery. Pharmacokinetic studies suggest that weak lipophilic drugs (eg, rocuronium) should be administered based on ideal body weight [3]. It is known that sugammadex has a weak lipophilic profile like rocuronium [4]. However, dose adjustment of sugammadex according to ideal body weight (IBW) or actual body weight (ABW) is still controversial. For lean patients, it was reported that 2 mg.kg<sup>-1</sup> sugammadex achieved a TOFR (train-of-four ratio) >0.9 in 1.4 (0.9-5.4) minutes in case of neuromuscular block with rocuronium [5]. Recurarization after insufficient doses of sugammadex has been previously reported [6]. Recurarization is life-threatening particularly in morbid obese patients secondary to concomitant comorbidities. Thus, calculation of appropriate sugammadex dose for morbidly obese patients should be clarified as soon as possible. Underdosing of the drug may be more dangerous than overdosing, further supporting the requirement for optimal dose calculation. In our prospective study, we compared the reversal of neuromuscular blockade and cognitive function recovery in morbidly obese patients after laparoscopic sleeve gastrectomy who received different doses of sugammadex according to ideal body weight (IBW), corrected body weight (CBW) or actual body weight (ABW).

## Material and Methods

The study was approved by the Ethical Committee of Turkish Pharmaceuticals and Medical Devices Agency, Trial Number: E-14-209/2014. Written informed consent was obtained from all participants. Sixty morbidly obese patients (BMI >40 kg.m<sup>-2</sup>) undergoing bariatric surgery were included in this prospective randomized study. Exclusion criteria included history of neuromuscular disease, use of drugs interfering with neuromuscular blocking agents, and severe cardiopulmonary or renal diseases. Patients were randomly divided into three groups as follows: 1) those receiving sugammadex based on ideal body weight (IBW), 2) those receiving sugammadex based on corrected body weight (CBW), 3) those receiving sugammadex based on actual body weight (ABW). Randomization was maintained using sealed envelope technique by a blinded investigator.

Calculations were corrected as follows [7]:

IBW (for men) = Height (cm) - 100;

IBW (for women) = Height (cm) - 105;

CBW = IBW + [(ABW - IBW) x 0.4]

All demographic parameters of the patients were recorded. Throughout the study period, routine monitoring was used (automated blood pressure cuff, electrocardiography, pulse oximetry, capnography) and the results were recorded. Intraoperative bispectral index (BIS) monitoring was recorded. Neuromuscular transmission was monitored in accordance with good clinical practice recommendations [8]. For neuromuscular

monitoring, the study arm was immobilized and temperature was maintained between 35.5-37°C. Surface electrodes were placed on the wrist as described in the acceleromyography user manual to monitor the blockade of adductor pollicis muscle (TOF-Watch S, Organon Ltd., Oss, Netherlands).

Preoxygenation was used for three minutes before anesthesia induction. TBW midazolam (0.02 mg.kg<sup>-1</sup>), TBW fentanyl (2 mcg.kg<sup>-1</sup>), and TBW (2 mg.kg<sup>-1</sup>) propofol were used for anesthesia induction. TOF calibration was performed after BIS value dropped below 60. Then, the neuromuscular blocking agent (rocuronium 0.6 mg.kg<sup>-1</sup> IBW) was administered before tracheal intubation. The evoked response was measured after TOF stimulation (four pulses of 0.2 ms duration at a frequency of 2 Hz) every 20 seconds throughout the procedure. Total intravenous anesthesia (intravenous 200 mcg.kg<sup>-1</sup>.min<sup>-1</sup> IBW propofol and 0.02 mcg.kg<sup>-1</sup>.min<sup>-1</sup> IBW remifentanyl infusion) was used for maintenance in order to achieve a BIS level below 60. Additional 10 mg rocuronium was administered if a T2 twitch reappeared in a TOF.

After the completion of surgery, all hypnotic infusions were stopped. BIS and neuromuscular blockage level were recorded. Sugammadex (2 mg.kg<sup>-1</sup>) according to their own groups was administered for neuromuscular block reversal. The timing variables were also recorded including time to reach a TOF >0.9 (neuromuscular reversal time), time to extubation (extubation time), time to reach a BIS >80 (cortical recovery time), time to eye opening, time to first verbal answer, time to orientation. For the first verbal answer, the question "Do you have pain?" was directed to the patients and the time to a meaningful verbal answer was recorded. The time to orientation time was established when the patients were able to tell the exact place and the date.

Tracheal extubation was performed when the patients were able to breathe on their own and tidal volume was persistently greater than 8 ml.kg<sup>-1</sup> IBW. Neuromuscular function monitoring was maintained in the post-anesthesia care unit for postoperative recurarization. PACU nurses were blinded to the study and they used specific routine discharge protocols for transferring the patients to the surgery ward.

### Statistical Analysis

In line with previous similar experiments in literature, a power analysis was performed which showed that 20 participants would be required in each group to observe differences in corresponding variables with 80% power. Differences in study parameters among three groups were analyzed using the Kruskal-Wallis test. The Mann-Whitney U test was used for dual comparisons of the groups. For all tests, the statistical significance value was set as p <0.05. The Kruskal-Wallis and Mann-Whitney U tests were performed using SPSS 20.0 (SPSS Inc., Chicago, IL).

## Results

The demographic characteristics of the patients are shown in Table 1. Patients in the three groups did not differ in age and actual body weight. Height was greatest in the IBW group (p=0.043) and BMI was lowest in Group IBW (p=0.035). Consistent with greater height values, calculated IBW and CBW values were highest in Group IBW (p=0.048 and 0.049,

respectively). There was no difference in surgery time between groups (p=0.151) (Table 1).

**Table 1.** Patient and Surgery Characteristics

	Group ABW (n=20)	Group CBW (n=20)	Group IBW (n=20)	p
Age (yr)	40.9±11.4	45.3±11.3	40.5±11.5	0.292
Gender (n) (M/F)	2/18	1/19	5/15	0.166
Height (cm)	161.0±7.0	161.3±7.9	166.9±8.8	0.043
ABW (kg)	126.5±14.5	121.5±29.1	129.1±18.4	0.680
CBW (kg)	84.5±9.05	82.2±13.5	89.4±12.5	0.049
IBW (kg)	56.8±8.2	56.5±8.8	63.2±10.5	0.048
BMI (kg.m-2)	48.7±5.6	46.5±12.4	46.3±5.0	0.035
Total Dose of				
Rocuronium (mg)	71.5±19.4	65.4±16.0	74.4±16.4	0.196
Sugammadex Dose (mg)	252.7±29.5	164.2±28.0	126.1±21.4	0.000
Surgery Time (min)	177.7±82.3	162.7±61.1	187.5±57.0	0.151

Values are demonstrated as mean ± standard deviation. M/F: Male/Female, ABW: Actual body weight, BMI: Body mass index, CBW: Corrected body weight, IBW: Ideal body weight

**Table 2.** Comparison of recovery times according to groups

	Group ABW (n=20)	Group CBW (n=20)	Group IBW (n=20)	P
Time to TOFR of 0.9 or more (sec)	137.05±106.10	170.45±146.16	202.65±79.90	0.05
Time to BIS 80 or more (sec)	160.65±81.53	231.60±99.08	290.95±178.70	0.024
Time to eye opening (sec)	180.60±112.03	258.55±169.94	262.30±130.34	0.102
Time to verbal answer (sec)	266.75±149.43	346.10±189.64	413.75±181.61	0.026
Time to orientation (sec)	313.40±189.81	387.10±210.94	517.80±291.13	0.028

Values are demonstrated as mean ± standard deviation.

The rocuronium doses that were administered for induction and maintenance of anesthesia were analyzed cumulatively and the total dose of rocuronium did not differ among three groups (p=0.196). The recovery times are shown in Table 2. Except for eye opening time which did not differ statistically between groups, all of the others were different between groups. The time to TOFR of 0.9, time to extubation was shortest in Group ABW and these times were longest in Group IBW (p=0.05, p=0.018, respectively). Cognitive recovery markers differed significantly among groups. The time to reach a BIS level above 80 was 160s in Group ABW, 231s in Group CBW and 290s in Group IBW (p=0.024). Time to the first verbal answer to the questions and time to orientation were significantly longest in Group IBW and shortest in Group ABW (p=0.026, 0.028, respectively). There were no complications associated with sugammadex injection. As expected to the study protocol, administered sugammadex doses were significantly different among groups (p≤0.001). With regard to the time to TOFR of 0.9 and time to extubation, one patient in Group ABW (480s, 490s, respectively) and one patient in Group CBW (753s, 800s, respectively) had more than

two-fold greater mean values of their own groups. None of the patients in Group IBW reached a time to TOFR of 0.9 or extubation time which was more than two-fold greater than the mean time of the group. Among the three groups, none of the patients had delayed discharge from PACU secondary to respiratory complications. None of the patients needed additional sugammadex doses for recovery from residual neuromuscular block.

**Discussion**

Definite fast and safe recovery methods for morbidly obese patients are still controversial. These patients are susceptible to various postoperative adverse events. Especially inability to maintain airway, hypoventilation and residual neuromuscular block are critical respiratory events [9,10]. Obese patients have a higher incidence of residual curarization compared to non-obese patients [9]. These findings led clinicians to prefer sugammadex rather than neostigmine for recovery of obese patients because it is known that neostigmine does not exactly prevent residual curarization. Gaszynski et al. compared the recovery profile of sugammadex and neostigmine in obese patients. Recovery times were significantly longer in the neostigmine group. In that study corrected body weight was used for sugammadex administration. Although they used a different method from ours to maintain anesthesia with desflurane, the times to TOFR of 0.9 observed in Group CBW were comparable [10]. Time to TOFR of 0.9 was 164s in that study and 170s in present study. Both studies did not demonstrate residual curarization event with this dosing regimen of sugammadex. The ideal dosing regimen for the administration of sugammadex to obese patients is still unclear. While the present study was randomized using sealed envelope technique, patients with BMI >40kg.m-2 were included to ensure having morbidly obese patients in the study. Also, the same surgical technique (laparoscopic sleeve gastrectomy) was included in the study to avoid adverse effects of other factors on patient recovery. Using the same surgical team, the operation time was not different between groups. It should be noted that the total rocuronium dose was not different between groups either. These important factors which may affect the recovery time were eliminated during the assessment of the study. The anesthesia maintaining agent and the method used for its monitoring is another factor that affects recovery profile. Rex et al. compared the recovery profile of sugammadex in non-obese patients undergoing surgery under maintenance anesthesia with sevoflurane or propofol in. No difference was reported in recovery times between groups [11]. However, studies on the reversal of rocuronium with edrophonium or neostigmine reported faster recovery with propofol compared to sevoflurane [12,13]. Siampalioti et al. reported faster extubation times with propofol versus sevoflurane in super obese patients. In the light of these reports, we preferred a total intravenous anesthesia with propofol rather than inhaler anesthesia in the present study. BIS monitoring was used to achieve standardized anesthesia depth not to alter cognitive recovery times. Studies with obese patients reported that BIS monitoring achieves safe and effective anesthesia depth and uneventful recovery profile with propofol infusion [14,15].

The present study showed that sugammadex administration based on IBW results in statistically significantly longer neuromuscular block reversal times. Drug dosage according to actual body weight resulted in the shortest neuromuscular block reversal times. As an additional contribution to the literature, the current study showed that sugammadex has an accelerator effect on cognitive recovery times. Time to reach a BIS level above 80, time to achieve first verbal answer from the patient and time to get postoperative orientation were shortest in Group ABW. Thus, in proportion to incremental sugammadex dosage, patients achieve cognitive recovery in a shorter time. The present study is the first prospective study on additional effects of sugammadex on cognitive recovery profile. Sugammadex has a lipophilic core and a hydrophilic exterior which belongs to the group of weak lipophilic drugs [4]. It was suggested that weak lipophilic drugs like rocuronium should be dosed on the basis of IBW rather than ABW in clinical practice [3]. However, studies on atracurium blockade in obese patients reported conflicting findings about drug dosing regimen [16,17]. Therefore, pharmacokinetic effects of the drugs might be distinctive in obese patients. Van Lackner et al. concluded that IBW calculations for sugammadex dosage may be safe but they recommended IBW+ 40% for optimization of reversal. The absence of data on rocuronium doses and surgery times precluded direct comparisons of their results with ours. Both studies administered sugammadex at moderate neuromuscular block with rocuronium. The mean BMI value in the present study was higher in Group IBW compared to that observed in Van Lackner's study but extubation time (311 vs 318s) and time to TOFR of 0.9 (202s vs 188s) were comparable [18]. Approved dosing regimen for moderate rocuronium-induced neuromuscular block is 2 mg/kg-1. Dose-finding studies have reported that time to reversal shortens with increased doses of sugammadex [19]. Our results were consistent with these findings. Time to TOFR of 0.9 and time to extubation decreased with increased drug doses. Cognitive recovery times (time to achieve a BIS above 80, time to get first verbal answer, time to orientation) exhibited a similar pattern with neuromuscular recovery times. It should be mentioned that in statistical analyses with pairwise comparisons, main variable differences were observed between Group IBW and Group ABW. Pairwise comparisons did not demonstrate any differences between Group IBW-Group CBW or Group ABW-Group CBW with respect to neuromuscular block reversal times or cognitive recovery times. These results show that the specific recommendation for sugammadex dose adjustment according to CBW and IBW may be equally inappropriate for neuromuscular reversal.

Slow responders were reported in dosing studies on lean individuals with sugammadex [20]. In the present study, two slow responders were identified (one in Group ABW and one in Group CBW). Additionally, it was recently reported that the recovery of the TOFR to 0.9 was not enough to achieve optimum reversal in obese patients. Upper airway obstruction may still occur in outlier patients with this TOFR. Thus, a TOFR threshold of 1.0 is now recommended [21,22].

### Conclusion

Even if the present study did not identify any recurarisation with defined sugammadex doses, slow responders and outliers

should be considered in morbidly obese population. Increased doses of sugammadex showed faster and more effective neuromuscular and cognitive recovery profiles. We suggest that TBW might be more appropriate for calculating sugammadex dose for safe and effective reversal of moderate rocuronium-induced neuromuscular block in morbidly obese patients.

### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

### Funding: None

### Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

### References

- Balsiger BM, Murr MM, Poggio JL, Sarr MG. Bariatric surgery: surgery for weight control in patients with morbid obesity. *Med Clin North Am.* 2000;84(2):477-89.
- Nguyen NT, Wolfe BM. The physiologic effects of pneumoperitoneum in the morbidly obese. *Ann Surg.* 2005;241(2):219-26.
- Leykin Y, Pellis T, Lucca M, Lomangino G, Marzano B, Gullo A. The pharmacodynamic effects of rocuronium when dosed according to real body weight or ideal body weight in morbidly obese patients. *Anesth Analg.* 2004;99(4):1086-9.
- Ingrande J, Lemmens HJ. Anesthetic pharmacology and the morbidly obese patient. *Curr Anaesthesiol Rep.* 2013;3(1):10-7.
- Blobner M, Eriksson LI, Scholz J, Motsch J, Della Rocca G, Prins ME. Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. *Eur J Anaesthesiol.* 2010;27(10):874-81.
- Eleveld DJ, Kuizenga K, Proost JH, Wierda JM. A temporary decrease in twitch response during reversal of rocuronium-induced muscle relaxation with a small dose of sugammadex. *Anesth Analg.* 2007;104(3):582-4.
- De Baerdemaeker LE, Mortier EP, Struys MM. Pharmacokinetics in obese patients. *Contin Educ Anaesth Crit Care Pain.* 2004;4(5):152-5.
- Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J. 8th International Neuromuscular Meeting: Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. *Acta Anaesthesiol Scand.* 2007;51(7):789-808.
- Gaszynski T, Jakubiak J, Szlachcinski L, Gaszynski W. Administration of neostigmine does not prevent from post-operative residual curarisation in morbidly obese patients. *Eur J Anaesthesiol Suppl.* 2008; 25:137.
- Gaszynski T, Szweczyk T, Gaszynski W. Randomized comparison of sugammadex and neostigmine for reversal of rocuronium-induced muscle relaxation in morbidly obese undergoing general anaesthesia. *Br J Anaesth.* 2012;108(2):236-9.
- Rex C, Wagner S, Spies C, Scholz J, Rietbergen H, Heeringa M, et al. Reversal of neuromuscular blockade by sugammadex after continuous infusion of rocuronium in patients randomized to sevoflurane or propofol maintenance anaesthesia. *Anesthesiology.* 2009;111(1):30-5.
- Zhou TJ, Chiu JW, White PF, Forestner JE, Murphy MT. Reversal of rocuronium with edrophonium during propofol versus sevoflurane anaesthesia. *Acta Anaesthesiol Scand.* 2001;45(2):246-9.
- Reid JE, Breslin DS, Mirakhur RK, Hayes AH. Neostigmine antagonism of rocuronium block during anaesthesia with sevoflurane, isoflurane or propofol. *Can J Anaesth.* 2001;48(4):351-5.
- Siampalioti A, Karavias D, Zotou A, Kalfarentzos F, Filos K. Anaesthesia management for the super obese: is sevoflurane superior to propofol as a sole anesthetic agent? A double-blind randomized controlled trial. *Eur Rev Med Pharmacol Sci.* 2015;19(13):2493-500.
- Pandazi A, Bourlioti A, Kostopanagiotou G. Bispectral Index (BIS) monitoring in morbidly obese patients undergoing gastric bypass surgery: experience in 23 patients. *Obes Surg.* 2005;15(1):58-62.
- Weinstein JA, Matteo RS, Ornstein E, Schwartz AE, Goldstoft M, Thal G. Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. *Anesth Analg.* 1988;67(12):1149-53.
- Kirkegaard-Nielsen H, Helbo-Hansen HS, Lindholm P, Severinsen IK, Pedersen HS. Anthropometric variables as predictors for duration of action of atracurium-induced neuromuscular block. *Anesth Analg.* 1996;83(5):1076-80.
- Van Lancker P, Dillemans B, Bogaert T, Mulier JP, De Kock M, Haspelslagh M.

*Ideal versus corrected body weight for dosage of sugammadex in morbidly obese patients. Anaesthesia. 2011;66(8):721-5.*

19. Mirakhur RK. Sugammadex in clinical practice. *Anaesthesia. 2009;64(Suppl.1):45-54.*

20. Kleijn HJ, Zollinger DP, van den Heuvel MW, Kerbusch T. Population pharmacokinetic pharmacodynamic analysis for sugammadex-mediated reversal of rocuronium-induced neuromuscular blockade. *Br J Clin Pharmacol. 2011;72(3):415-33.*

21. Llauradó S, Sabaté A, Ferreres E, Camprubí I, Cabrera A. Sugammadex Ideal Body Weight Dose Adjusted by Level of Meeting Abstracts in Laparoscopic Bariatric Surgery. *Anesthesiology. 2012; 117(7): 93-98.*

22. Kotake Y, Ochiai R, Suzuki T, Ogawa S, Takagi Ozaki M, Nakatsuka I, et al. Reversal with sugammadex in the absence of monitoring did not preclude residual neuromuscular block. *Anesth Analg. 2013;117(2):345-51.*

**How to cite this article:**

Dilsen Hatice Ornek, Aysu Hayriye Tezcan, Hulya Ozden Terzi, Baris Doğu Yildiz. Dosage of Sugammadex in morbidly obese patients. *Ann Clin Anal Med 2020;11(Suppl 1): S52-56*